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10/691,928	10/23/2003	Jay A. Goldstein	JAG 100	1611

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/691,928	GOLDSTEIN ET AL.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1 and 3-5 have been amended in an amendment filed 06 December 2007. As a result, claims 1-17 are pending and are examined herein on the merits for patentability. No claim is allowed at this time.

Withdrawn Rejections

The previous rejections not repeated within this office action are withdrawn by the examiner.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1 and 8-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Quigley et al.

Quigley et al. disclose a lotion having the following composition: water, the solvent propylene glycol, the humectant glycerin, the emulsifier glyceryl monostrearate, the preservatives benzyl alcohol and sodium benzoate, the base triethanolamine, a steroid from about 0.01 to 0.1 wt.%, preferably betamethasone dipropionate

(betamethasone dipropionate lotion is a class 5 lower-mid strength potency steroid at 0.02 wt.%, see column 5, line 31), and the antifungal butenafine HCl (column 11, lines 3-23; Table G). Quigley et al. also discloses the antifungal compounds include terbinafine and naftifine (column 4, lines 4-51). Quigley et al. further disclose that steroids that penetrate the skin cause undesirable side effects (column 1, lines 28-29), and penetration of the epidermis with the test formulations proved to be significantly lower than that shown for Lotrisone formulation (column 18, lines 38-42). Therefore, Quigley et al. disclose a lotion composition comprising all the limitations of the instant claims and discloses the desire to minimize penetration of the steroid through the epidermis in an attempt to avoid undesirable side effects. Although the composition listed in Table G of Quigley et al. discloses butenafine as the preferred antifungal, the disclosure recites three antifungal agents of particular interest: terbinafine, naftifine and butenafine (col. 3, l. 63 - col. 4, l. 51). Therefore, one of ordinary skill in the art would immediately envisage a composition comprising all the ingredients listed in Table G, except substituting terbinafine or naftifine for butenafine.

Response to Arguments

Applicant's arguments filed 06 December 2007 have been fully considered but they are not persuasive. Applicants argue on page 10 that one would expect to see lower efficacy for the formulations in Quigley et al. when incorporating a low potency steroidal anti-inflammatory, and greater efficacy with stronger steroidal anti-inflammatories, which clearly teaches away from the claimed formulation which

specifies that the steroidal anti-inflammatory has a low to low-medium potency in order to avoid local side effects and yet has excellent efficacy.

However, the examiner does not find support for the allegation that Quigley et al. teach away from using a steroidal anti-inflammatory that has a low to low-medium potency. Quigley et al. disclose that the combination of the antifungal agent and the steroid demonstrates a synergistic effect (col. 2, ll. 16-19), and the amount of the steroid required for a therapeutically effective amount will vary depending upon its potency (col. 5, ll. 53-56). Quigley et al. further discloses a lotion formulation comprising 0.01 to 0.1 wt.% steroid, preferably betamethasone dipropionate, in combination with 1 to 3 wt.% of an antifungal, preferably butenafine hydrochloride salt (col. 11, ll. 1-38). The examiner directs attention to col. 5, l. 31, wherein Quigley et al. disclose that betamethasone dipropionate in the form of a lotion is a class 5 (low-medium) potency steroid. Furthermore, "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." See MPEP 2123(I) and (II).

2. Claims 1-3, 8-13 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 1 159 956 A2 (hereinafter Burnett et al.).

Burnett et al. disclose compositions comprising an antifungal (i.e. ketoconazole and like related imidazole antifungal agents), a steroidal anti-inflammatory (i.e. desonide), a solvent/penetration enhancer (i.e. propylene glycol), a humectant (i.e.

glycerin and/or sorbitol), an emollient (stearyl alcohol or cetyl alcohol), dibasic sodium phosphate, PPG-15 stearyl ether, and benzoic acid (abstract; paragraphs [0002], [0008], [0009], [0012]-[0019]; and Tables 1-4). Burnett et al. further disclose that topical compositions known in the prior art comprise an antifungal and steroid have a pH of between 2.5 and 6 (paragraph [0006]). Burnett et al. further disclose treating *Trichophyton rubrum* (i.e. tinea corporis, tinea cruris and tinea pedis) with the compositions of their invention (paragraph [0032]).

It is noted that Burnett et al. disclose the required penetration enhancer/solvent selected from the group consisting of alcohol, propylene glycol, or a combination thereof (paragraph [0012]), wherein the instant invention requires the composition does not cause the steroids to penetrate the skin and cause undesirable side effects (instant claim 1). However, propylene glycol is a solvent listed in the instant claim 12. Also, Burnett et al. disclose that the compositions of their invention demonstrate targeted delivery of desonide to the skin (cutaneous compartments) with greater amounts of the medicaments in the intended sites of the epidermis and dermis (paragraph [0036]). Burnett et al. state that the compositions demonstrated positively less permeation through the skin into the receptor that could clinically translate into lower systemic toxicity (paragraph [0037]). Therefore, even though Burnett et al. refer to the solvent propylene glycol (same as instantly claimed) as a penetration enhancer/solvent, they clarify the desire to prevent permeation of the medicament through the skin and into the receptor, resulting in diminished side effects. Thus, the compositions of Burnett et al. are disclosed not to penetrate through the skin and into the receptor.

Response to Arguments

Applicants argue on page 11 that Burnett et al. do not disclose or suggest compositions containing a therapeutically effective amount of an antifungal compound for treating a fungal disease or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation.

However, the examiner respectfully directs attention to Tables 1-4 wherein Burnett et al. disclose formulations comprising up to 2 wt.% ketoconazole and 0.05 wt.% desonide. Instant claim 5 is drawn to a topical antifungal composition comprising 0.01 to 5.0 wt.% desonide; and the instant specification defines suitable antifungal agents to include ketoconazole (pg. 4, l. 7), wherein the antifungal is present at 0.01 to 5.0 wt.% (pg. 7, ll. 23-24). Therefore, the compositions disclosed by Burnett et al. comprising up to 2 wt.% ketoconazole and 0.05 wt.% desonide would necessarily be a therapeutically effective amount of each component.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 2, 3, 7 and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quigley et al. as evidenced by the instant specification.

Applicant claims:

Applicant claims a topical antifungal composition comprising an antifungal, a low to low-medium potency non-halogenated steroidal anti-inflammatory (listed in claim 7), and a carrier that does not afford penetration of the steroid through the skin causing undesirable side effects. Applicant further claims a method of treating a fungal disease (listed in claim 16) comprising administering the aforementioned composition with a thin application of the composition two times per day to the affected areas, wherein the patient may comprise a child of under 10 years old (claim 15).

Determination of the scope and content of the prior art

(MPEP 2141.01)

Quigley et al. teach a lotion composition comprising an antifungal, a low-mid strength steroidal anti-inflammatory (0.01 to 0.1 wt.% betamethasone dipropionate lotion), and excipients that don't afford steroidal penetration of the epidermis, as discussed above. Quigley et al. also teach a cream formulation comprising the same

excipients as listed in the aforementioned lotion, wherein the steroid is preferably from 0.01 to 0.1 wt.%, and is preferably betamethasone dipropionate (column 7, line 38 through column 8, line 28; Table A).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Quigley et al. do not explicitly teach an explicit composition comprising a low to low-medium potency steroidal anti-inflammatory having a structure shown in instant claim 2, nor those selected from the group listed in claim 7. However, Quigley et al. teach desonide cream 0.05% as a suitable steroid anti-inflammatory for use in the present invention (column 5, line 45; and column 8, lines 23-24). Desonide is a species within the generic structure of steroid anti-inflammatory compounds shown in instant claim 2 (instant claims 2-5).

Also, Quigley et al. do not explicitly teach applying the composition two times per day to the affected area. However, Quigley et al. teach that routine experimentation by one of ordinary skill in the art would be able to determine the effective amount of application of the topical composition (column 7, lines 11-24).

Furthermore, Quigley et al. do not teach applying the composition to a child of under 10 years old. However, Quigley et al. teach desonide cream 0.05% as a suitable steroidal anti-inflammatory and the instant specification teaches that desonide is a class 6 non-fluorinated topical corticosteroid which has been available for more than two decades and clinical trials have shown that desonide is effective and safe for treating children having dermatosis or other skin diseases.

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to use desonide cream 0.05% in the cream formulation taught by Quigley et al. because Quigley et al. teach that desonide cream 0.05% is a suitable steroidal anti-inflammatory for use in combination with an antifungal. One of ordinary skill in the art would have been motivated to use desonide cream 0.05% in the cream formulation of Quigley et al. because desonide is a class 6 non-fluorinated topical corticosteroid which has been available for more than two decades and clinical trials have shown that desonide is effective and safe for treating children having dermatosis or other skin diseases, as evidenced by the instant applications specification. Also, it would have been routine experimentation for a person of ordinary skill in the art to determine the number of applications of the cream formulation of Quigley et al. in order to achieve desired results in treating fungal diseases.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants argue on pages 14 and 15 applicants have selected not only a small number of the steroidal anti-inflammatories taught by Quigley et al., but also a subset of

the concentration range taught by Quigley et al. Applicants further argue that Quigley et al. do not teach each element of the claims.

However, the examiner respectfully argues that Quigley et al. specifically teach a lotion comprising 0.01 to 0.1 wt.% betamethasone dipropionate and 1-3 wt.% butenafine (col. 11, ll. 1-38, Table G). Quigley et al. also teach a cream comprising 0.01 to 0.1 wt.% betamethasone dipropionate and 1-3 wt.% butenafine (col. 7, l. 38 - col. 8, l. 28, Table A). Quigley et al. further teach that desonide cream is a class 6 potency steroidal anti-inflammatory. Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute desonide cream in the place of betamethasone dipropionate cream with the expectation that the steroidal anti-inflammatory would be therapeutically effective.

2. Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Burnett et al. in view of U.S. Patent No. 5,219,877 (hereinafter Shah et al.).

Applicant claims:

Applicant claims a topical antifungal composition comprising 0.1 to 5.0 wt.% clotrimazole, 0.01 to 5.0 wt.% desonide, and a carrier that does not afford penetration of the steroid through the skin causing undesirable side effects.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Burnett et al. teach compositions comprising preferably about 0.05 wt.% desonide ([paragraph [0019]) and preferably about 2 wt.% of an imidazole antifungal

agent (paragraphs [0014] and [0019]), wherein the composition does not permeate through the skin, as discussed above.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Burnett et al. teach the antifungal agent includes ketoconazole, miconazole, itraconazole, metronidazole, elubiol, and like related imidazole antifungal agents known to those of skill in the art, but do not teach the antifungal agent to comprise clotrimazole as instantly claimed. However, Shah et al. teach formulations suitable for treatment of tinea capitis, tinea corporis, tinea cruris, and tinea pedis comprising 0.2 to 2.0% w/v of an imidazole antifungal agent, such as clotrimazole, and further comprising an anti-inflammatory steroid including desonide (column 1, lines 6-14; and column 3, lines 43-65). Shah et al. further teach that commercially marketed 1 wt.% clotrimazole exhibits very low permeation rates through skin, and cannot be effectively used for treatment of deep skin fungal infections (column 6, lines 3-34). Thus, the commercially marketed clotrimazole does not permeate through the skin.

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to use clotrimazole as the imidazole antifungal agent in the compositions of Burnett et al. because Shah et al. teach clotrimazole as a suitable imidazole antifungal for treating tinea capitis, tinea corporis, tinea cruris, and tinea pedis. One would have been motivated to use clotrimazole as the antifungal agent

because Burnett et al. teaches the desire to reduce the amount of skin permeation in order to reduce side effects, and Shah et al. teach that commercially marketed 1 wt.% clotrimazole does not permeate through the skin.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants argue on page 16 that Shah et al. teach away from the claimed compositions by disclosing that strong steroidal anti-inflammatories cause undesirable side effects such as skin atrophy, rebound phenomenon, and telangiectasia and low potency steroidal anti-inflammatories are not effective in providing fast relief from inflammatory symptoms (col. 4, ll. 3-11).

However, the examiner respectfully directs attention to col. 3, ll. 54-59 and 65 wherein Shah et al. teach that steroidal anti-inflammatories suitable for their invention includes desonide, which is the instantly claimed steroid, and is preferably used in conjunction with an antifungal agent, such as clotrimazole. Also, Shah et al. was merely used to show that clotrimazole is an effective antifungal agent that can be used as the imidazole antifungal agent in the composition of Burnett et al.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-272-9924. The examiner can normally be reached on 8:30 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/Mina Haghighatian/
Primary Examiner
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